Details online

Methodological description: A prospective multi-center comparative study**.**

Patient inclusion: Average risk individuals referred for screening colonoscopy or individuals with a polyp detected on previous colonoscopy or CT colonography referred to one of the three tertiary gastroenterology centers for polypectomy.
Patient exclusion: Patients with dysphagia or odynophagia, Crohn's disease, previous bowel surgery, strictures or previous radiotherapy, morbid obesity (BMI>40), contrast medium hypersensitivity or renal failure.

IRB/registration:
The study was approved by IRB in all sites, as well as by the national ethics committee of the Israeli Ministry of Health. All patients signed an informed consent form.

Main outcomes:
Safety and efficacy of a novel prep-less X-ray imaging capsule for polyp detection compared to colonoscopy.

Study approach:

Device and technique: The system (Check-Cap LTD., Israel) has already been described[1, 2]. Briefly, X-ray beams are emitted in all directions as the capsule scans the colon. Ingested contrast media provides contrast to the colon wall and differentiates it from stool. The capsule senses Compton backscattered photons, attenuated by the contrast agent mixed with the colon contents, and X-ray fluorescence photons emitted from the contrast agent. These signals are processed by on-board electronics and software to estimate the distance from the capsule to the colon wall, allowing 3D image reconstruction of the colon lumen and outer wall. A simultaneous track of the capsule position and orientation along the colon is generated by 3D accelerometers and magnetometers, with an accuracy of +/- 1 cm, even when patients are in motion. This allows the clinician to localize findings correctly toward planning subsequent intervention. Novel pressure sensors have been incorporated in the current system version, allowing accurate timing of capsule entrance into the caecum as well as suggesting contact of the capsule with a protruding lesion such as a polyp (Figure 1 in main text). Novel temperature sensors identify capsule expulsion and activate a signal to notify the patient. All imaging and telemetric data are sent to an external control unit that is attached on the patient's back. Besides recording the data, this unit tracks the capsule position and orientation, commands and communicates data to the capsule. The capsule and recording system are designed to operate for 100 hours. Following the procedure, data from the tracking unit is downloaded to a dedicated PC-based workstation. This station manages patient information, displays 2D and 3D colon reconstruction, and generates a procedure report.
Colon scanning and imaging: The clinical efficacy of the capsule imaging system is determined primarily by two factors. First, the capsule must detect a polyp when it scans it. This parameter was studied and optimized in the laboratory prior to this study, using phantom colon models with different sizes of artificial polyps. A lab performance of 100% for correctly imaging polyps greater than 6 mm was achieved[1, 2]. The second parameter is colon imaging, expressed as the percentage of total colon surface area adequately scanned by the capsule. This parameter required the development of a scan control algorithm (SCA) that was optimized based on acquiring sufficient clinical data and capsule motility statistics. Since our previous report[1], the SCA has been embedded in the system control unit. This makes the system completely autonomous, allowing all procedures to be performed independently by patients in their familiar environment.
Procedure: All patients underwent the capsule procedure and concomitant FIT (OC-Light, Eiken, Japan; cut-off was 10 μgHg/ gr stool) followed by colonoscopy. FIT was chosen for comparison to

capsule performance since it is the standard of care in Europe for CRC screening[3]. FIT kits were accompanied by written and verbal instructions, and FIT results were visually recorded and collected. After swallowing the capsule, iodine-based contrast agent (Iohexol, GE Healthcare, US) necessary for generating images (15 cc TID) was ingested. A tablespoon of fiber supplement was added to meals to improved capsule motility. Patients continued their normal home and work routine and reported their comfort level. Capsules were collected by patients and submitted for inspection. Colonoscopy was performed after capsule expulsion as the gold reference, with removal of all visualized polyps.

Total transit time [TTT] was measured from capsule ingestion to excretion. The TTT is the sum of 3 distinct time segments: until the cecum, within the cecum and distal to cecum until excretion.

Radiation dose: The total body dose was calculated in each case as a function of TTT and the total number of scans (when the collimator is open). In the protocol we estimated that the typical body dose would be ≈ 0.06 mSv.

Review and report: Two qualified gastroenterologists were trained to analyze capsule scans post-hoc, and served as independent reviewers. A reviewing forum consisted of at least one gastroenterologist and two expert imaging engineers that jointly reviewed all cases. This forum was completely blinded to the FIT and colonoscopy results of the study subjects. Suspected images were identified on 2D images and assessed using a series of questions that relate to image characteristics, mobility and pressure signals. Assessment was confirmed in 3D reconstruction. The output of the clinical review is a printed report with a clear decision (positive/negative) regarding all suspicious findings per patient. The anonymous colonoscopy reports including size and location of each polyp were compared to the capsule findings by a gastroenterologist who did not participate in the capsule review. In the cohort of patients with known polyps, findings from both previous colonoscopy and subsequent therapeutic colonoscopy were included in the statistical analysis. Sensitivity and specificity of the capsule findings were calculated with reference to FIT and colonoscopy. Results were analyzed as a function of the percentage of colon surface area effectively imaged by the scanning capsule.

Statistical analysis: Assuming large adenomas as target lesions for detection, a threshold of 30% sensitivity was selected for FIT as reference. To calculate the sample size for the study, 55% positive percent agreement (a surrogate for sensitivity since colonoscopy, which is not a true gold standard, is used as reference) was assumed for the capsule with 80% statistical power. Using MedCalc™ medical statistics software, and calculating single-sided proportion, the minimal sample size was calculated to be 27 patients with polyps. A total sample size of 40 subjects was set (27 with polyps) as the target sample size for statistical analysis. Analysis was performed on a per patient basis for the existence or non-existence of a finding suspected to be a polyp. This was compared to findings of FIT and colonoscopy performed per patient. For this process, two 'confusion' matrices were filed: capsule vs. FIT and capsule vs. colonoscopy. Colonoscopy was considered the gold reference and hence the values shown are percent agreement relative to colonoscopy.

Details of results

Endoscopy details

Sixty six patients (age 37-79 year, 40 male) were enrolled. Forty three had un-resected polyps (>10mm) and 23 were average risk with no prior colonoscopy. Forty five procedures were analyzed (68%). Dropouts included 13 technical failures and 8 physiological/anatomical outliers. Malfunction was caused by improper battery production (2 cases), rotation mechanism faults (2 cases), detector reading out of normal range, thus generating defective scanning data (2 cases), and track malfunction caused by production errors (3 cases). One case failed to 'reboot' after reset and did not recover back to normal operation. In two cases the concealment mechanism was left open following the scan completion. All technical malfunctions were investigated, their cause was identified, and manufacturing processes were amended to correct these defects. The physiological/anatomical

outliers included three subjects that failed to swallow the capsule and one subject in which capsule excretion was delayed >100 hours and was removed during colonoscopy. In two others sodium picosulfate was used to expedite the expulsion of non-functioning capsules. In all cases the TTT was less than 200 hours. In one case the capsule was not retrieved by the patient at the end of the procedure and was probably lost in the sewage. X-ray of the abdominal cavity confirmed capsule expulsion.

All patients continued their daily routine on normal diet. All capsules but one were collected and retrieved for inspection, and found to be intact and hermetically sealed. Infrequent adverse events, including soft stool (n=10), mild abdominal pain (n=5), headache (n=2) and rash under the back sticker (n=1) resolved spontaneously within a few hours. One serious adverse event (SAE) occurred: an abdominal wall hematoma not related to the device or capsule procedures.

Total radiation dose: The average calculated total body X-ray dose exposure was 0.051 mSv, slightly below the estimated 0.06 mSv.

Capsule transit time: Average TTT in all 63 ingested capsules was 52±32 hours. Average transit time of the three sections of the GI tract is shown in Table S1.

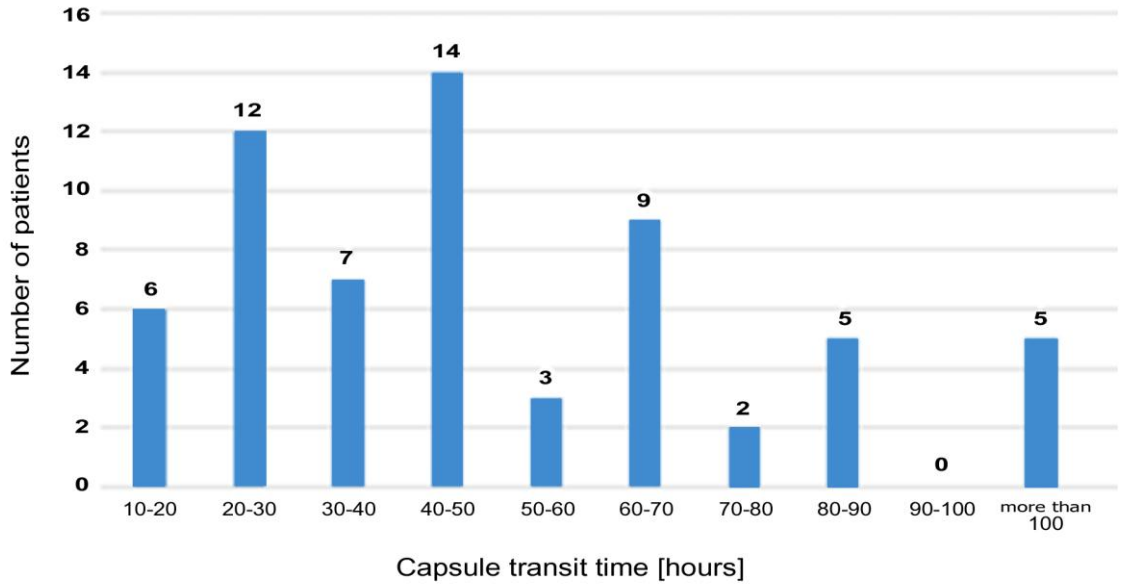
Table S1. Capsule transit times in the colon

	Total Transit Time	**Time to Caecum**	**Time in Caecum**	**Passage in Colon**
Average (*hours*)	52.3	15.9	16.8	16.5
Standard deviation	32.9	13.8	18.8	12.1

The standard deviation is quite high due to the considerable variability in bowel motility. The variability of the TTT is clearly presented in Figure S1. In four cases (4/66= 6%) the capsule was delayed for more than the set time, and in one additional case it was removed during colonoscopy.

FIT was returned by all 45 subjects that were analyzed. Fourteen were positive and 31 were negative. Sensitivity of the FIT for polyp detection was 37% with a specificity of 100%.

Figure S1: **Capsule transit times**. The plot shows the distribution of transit times, from ingestion to excretion, in all patients that ingested the capsule (63 in total).



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2. Kimchy Y, Lifshitz R, Lewkowitz S, Bertuccio G, Arber N, Gluck N, Pickhardt PJ. Radiographic capsule-based system for non-cathartic colorectal cancer screening. Abdom Radiol (NY) 2017;42:1291-1297.
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